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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,864	06/27/2005	Yuji Matsuzawa	Q88792	1045

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EXAMINER	
SULLIVAN, DANIEL M	

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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,864	MATSUZAWA ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-22 and 30-33* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 15-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 8 February 2008 in response to the Non-Final Office Action mailed 8 August 2007. Claims 1-11 and 15-22 were withdrawn from consideration and claims 12-14 and 23-29 were considered in the 8 August Office Action. Claims 10, 12 and 14 were amended, claims 13 and 23-29 were cancelled and claims 30-33 were added in the 8 February Paper. Claims 1-12, 14-22 and 30-33 are pending and claims 12, 14 and 30-33 are presently under consideration.

Response to Amendment and Arguments

Objection to and rejection of claims 13 and 23-29 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 **stands rejected** and newly added claims 30-33 **are rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a screening method for a compound which is capable of enhancing human adiponectin promoter activity, does not reasonably provide enablement for a screening method for a preventive and/or therapeutic medicine for diabetes, obesity, arteriosclerosis or insulin resistance syndrome. This rejection is

maintained for the reasons set forth in the 8 August Office Action, beginning at page 5, and herein below in the response to Applicant's arguments.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant submits that the state of the art at the time of filing demonstrates that activation of adiponectin transcription was an effective approach to treating the diseases selected from diabetes, obesity, arteriosclerosis, or insulin resistance syndrome. Applicant cites Maeda et al. (Nature Medicine, 2002,7:731-737) as teaching that adiponectin, a protein that is abundant in serum, is decreased in obese patients and those having type II diabetes, that murine diabetes is improved by treatment with adiponectin (left column, page 73 1) and that insulin resistance is improved upon expression of adiponectin using adiponectin knockout mice. In addition, Applicant cites Okamoto et al. (Circulation, 2002, 106:2767-2770) as demonstrating that atherosclerotic foci are decreased when adiponectin is expressed in apolipoprotein E (ApoE)-deficient mice, which exhibit atheromatous arteriosclerosis (Figure. 1). Applicant submits that in view of the guidance provided by the instant specification, and the state of the art at the time of filing as evidenced by Maeda et al. and Okamoto et al., it would be apparent to one of skill in the art that a compound which increases the expression of adiponectin is useful for the treatment of diabetes, obesity, arteriosclerosis, or insulin resistance syndrome and that in view of such data, one of skill in the art would realize that Applicant's claimed invention would function predictably as a surrogate endpoint.

These arguments have been fully considered but are not deemed persuasive in view of the record as a whole. It is first noted that Maeda et al. and Okamoto et al. references have not been

properly made of record in an IDS[1] or on a PTO-982. Therefore, the teachings have been considered only insofar as they are characterized in Applicant's remarks and in the specification. In the previous Office Action, the Office cites Díez et al. as teaching, "Testing these hypotheses [that adiponectin can be used to treat various conditions] is a challenge for future clinical research. Further investigations in patients with the above-mentioned states and other hypoadiponectinemic situations are required to clarify these aspects of the potential therapeutic applications of this fascinating adipocytokine." (Page 298, final two sentences.) Thus, the art teaches that, at the time the instant application was filed, adiponectin had not been established as an effective in the treatment or prevention of any condition. The Office further cites Wagner (2002) *Dis. Markers* 18:41-46 as teaching, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44); Frank *et al.* (2003) *Nature Rev.* 2:566-580 as teaching, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568); and Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 as teaching, "The development and validation of

[1] The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

In view of the record as a whole, one of skill in the art would not have viewed evidence of decreased adiponectin expression in obesity and type II diabetes and some evidence of improvement in experimental animals treated with adiponectin murine diabetes is improved by treatment with adiponectin as establishing that the method presently claimed is a validated model of diabetes, obesity, arteriosclerosis and insulin resistance syndrome such that one would recognize that the method can be used to screen for compounds useful to treat any of these diseases. The art cited in the previous Office Action clearly establishes that putative biomarkers must be validated and that "few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation" and that the therapeutic or prophylactic efficacy of adiponectin had not yet been verified for any of the syndromes recited in the claims at the time the application was filed. Given this high degree of unpredictability and the absence of any direct evidence to establish that expression in the transformant of the claims gene is a valid surrogate endpoint for therapeutic efficacy in the treatment of the syndromes recited in the claims, the basic premise underlying the claimed invention is no more than a theoretical possibility. This is not sufficient to meet the enablement requirement of 35 USC §112, first paragraph.

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing

> out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Genentech Inc. v. Novo* Nordisk A/S (CA FC) 42 USPQ2d 1001, 1005.

See also *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297 (Fed. Cir. 2005). (In response to Rasmusson's argument that the enablement requirement of section 112 does not mandate a showing of utility or, if it does, it mandates only a showing that it is "not implausible" that the invention will work for its intended purpose, the Court states, "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.")

In view of the foregoing, it would require undue experimentation to practice the invention claimed. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the claim amendments.

Claim Rejections - 35 USC § 103

Rejection of claims 12 and 14 under 35 U.S.C. 103(a) as being unpatentable over Dufaure-Gare et al. WO 00/26363 (made of record in the IDS filed 27 June 2005) is **withdrawn** in view of the amendment of the claims to require that the method includes transforming a first and second cell with an expression plasmid encoding PPARγ protein and an expression plasmid encoding a human RXRα protein. The art does not teach or suggest these limitations.

New Grounds Necessitated by Amendment

Claim Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim has been amended to recite only an intended use for the method claimed in claim 12. MPEP 2111.02 II. states, "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." (Citing *Pitney Bowes, Inc. v. Hewlett-*

Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999)). By logical extension, if the body of a base claim fully and intrinsically sets forth all of the limitations of the claimed invention, and a dependent claim merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the intended use recited in the dependent claim is not considered a limitation and is of no significance to claim construction with regard to claim scope. As the intended use recited in claim 14 does not materially alter the way that the method of claim 12 is carried out, the recitation of the intended use is not further limiting.

It is noted that although the recitation of the intended use is not viewed as further limiting, the recitation of an intended use in a claim does require that enablement for the claimed invention be considered in view of the recited use[2]. As these are separate issues, this objection in no way contradicts the enablement rejection discussed herein above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 14 and 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[2] See MPEP 2164.01(c) which states: "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)."

Claim 12 is indefinite in reciting "the nucleotide sequence represented by SEQ ID NO: 1". As the disclosure provides no guidance as to how a nucleotide sequence is "represented by" the SEQ ID NO: 1 sequence (e.g., the sequence comprises SEQ ID NO: 1, the sequence has the same function but not necessarily the same structure as the SEQ ID NO: 1 sequence, etc.) it is unclear what is within the scope of a nucleotide sequence represented by SEQ ID NO: 1. It is recommended that standard claim language such as "comprising the nucleotide sequence of SEQ ID NO: 1" be used if it is Applicant's intention that the DNA molecule comprise the entire sequence set forth in the application as SEQ ID NO: 1.

Claims 14 and 30-33 are indefinite insofar as they depend from claim 12.

Claims 30-33 are further indefinite in reciting, "said compound regulates..." Claim 12, from which claims 30-33 ultimately depend refers to two compounds (i.e., a test compound and a compound identified in the method as enhancing human adiponectin promoter activity). It is unclear whether the limitations recited in claims 30-33 are directed only to the compound identified as an enhancer of adiponectin promoter activity or whether the limitation applies to all of the compounds tested in the method. Therefore, the antecedent basis of the claim limitations and the metes and bounds of the claims as a whole are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 12, 14 and 30-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Iwaki et al. (2003) *Diabetes* 52:1655-1663. It is noted that Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Furthermore, as Iwaki et al. includes authors not named as inventors on the instant application, the publication is by another and qualifies as prior art under 35 USC § 103(a).

Iwaki et al. teaches a method comprising introducing into cells a reporter construct comprising the 5' flanking region of the human adiponectin gene from 908 bases upstream of the human adiponectin transcriptional start site, which, absent evidence to the contrary is the same as the promoter sequence in the plasmid p(-908)/LUC used in the instant working examples. Iwaki et al. further teaches cotransfecting expression vectors encoding human PPARγ and RXRα and assaying for the effects of an agent on expression of the reporter gene relative to expression in cells treated with vehicle alone. (See especially the paragraph bridging pages 1657-1658, Figure 1A and the caption thereto.) The method of Iwaki et al. comprises all of the elements of the method of the instant claim 12. Furthermore, as claim 14 merely recites an intended use for the method which does not materially alter the way the method is carried out, the method of claim 14 is also anticipated by Iwaki et al.[3] In addition, Iwaki et al. teaches the method wherein the cells are further transfected with a construct encoding LRH-1 according to the instant claim 33. (See especially the paragraph bridging the left and right columns on page 1659, Figure 5C and the caption thereto.) Finally, with regard to claims 30-32, Iwaki et al.

[3] It is noted that anticipation does not require that the prior art reference be enabling for an intended use recited in the claim. Therefore, the citation of Iwaki et al. against claim 14 in no way indicates that the claim is enabled for the recited use.

demonstrates that regulation of the adiponectin promoter by the compound tested therein (i.e., pioglitazone) involves each of PPARγ, RXRα and LRH-1, evidencing that, at least with respect to expression from the adiponectin promoter, pioglitazone regulates each of PPARγ, RXRα and LRH-1.

In view of the foregoing, the method of claims 12, 14 and 30-33 are anticipated by the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636